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- USSR -

by D. S. Sarkisov

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## FOREWORD

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## EXPERIMENTAL MODELS OF HUMAN DISEASES

-USSR-

Following is a translation of an article by D. S. Sarkisov in the Russian-language periodical Experimental'naya Khirurgiya (Experimental Surgery), Moscow, Vol. V, No. 1, January-February, 1960, pages 3-7.

Institute of Surgery imeni V. V. Vishnevskiy (Director-Prof. A. A. Vishnevskiy, Corresponding Member of the Academy of Medical Sciences of the USSR) of the Academy of Medical Sciences of the USSR.

So-called experimental models of diseases are frequently used for solving problems of etiology, pathogenesis and treatment of human diseases. This means the picture of some human disease reproduced in animals by specially developed methods. Experimental models of diseases are used for different purposes. In the hands of an experimenter they give unlimited material for studying the etiology and pathology of human diseases, for instance of arteriosclerosis, diffused glomerulonephritis, certain types of acute pneumonia, many infectious diseases, etc. Models are very important for experimental oncology; by inducing different tumors in animals we can study the chief mechanisms of malignant growth and can develop methods for combating tumors. Models of diseases are also very important for experimental pharmacology and chemotherapy where new preparations against cancer, hypertonic diseases, tuberculosis and other diseases are tested on animals.

Many difficulties stand in the way of reproducing human diseases in animals, and of using the models obtained correctly. As yet there are no clearly stated requirements and directions to guide us in developing models. There has been little discussion of the rules for selecting one or another model suitable for solving a specific problem confronting an experimental worker. In this article we will dwell on certain problems encountered in this field and demonstrate how they are being solved.

Under the expression "model of disease" we should understand the reproduction in animals of human diseases not only as nosological units with their etiological, pathogenic and clinicoanatomical specific character. This expression also includes: 1) models of individual diseases (hypertonic diseases, diabetis, nephritis); 2) models of general pathological processes (various forms of inflammation, dystrophy, etc.); 3) models of pathological conditions and complications characteristic of different diseases (cardiac failure, pulmonary edema, cerebral hemorrhage, infarct of the myocardium, etc); 4) models of functional disorders, which may develop in the course of one or another

disease (extrasystole, ciliary arrhythmia, polyuria, etc.). All the models mentioned above are widely used in experimental medicine. In each specific case, the choice of one or another model is determined by the purpose of the experiment. It is not always necessary to use a model reproducing wholly some nosological unit. For instance, to study the dynamics of an inflammation or the activity of a new anti-inflammation remedy, different models of this general pathological process are used - an aseptic, hyperergial or infectious pneumonia. In investigating biochemical processes in a fatty dystrophy of the myocardium, we can limit ourselves to simpler methods of its reproduction in animals (phosphorus intoxication, acute hypoxia) without turning to complicated models of diseases characteristic of this type of affection of the cardiac muscle (hypertonic disease, malignant anemia, valve failure, etc). To develop techniques for operative interventions in cardiac failure or to obtain acute or chronic cardiac insufficiency preceding failure, it is not necessary to reproduce specially an illness in animals which may give rise to complications of valvular incompetence or stenosis of the opening (rheumatism, septic endocarditis). This pathological condition can be caused by the simple mechanism of injuring the valves or by placing a constricting ring.

In cases where different problems of etiology, pathogenesis and, frequently, treatment of some disease are the object of research, it is usual to resort to its more complete model. With such a model the nearest relationship between man's diseases and animal's pathological process can be revealed and, consequently, it is possible to have a more complete adaptation of experimental data in the clinic. Thus, for instance, the dynamics of functional and morphological disturbances in an infarct of the myocardium can be studied by inducing this condition in a healthy animal, or in an animal in which a hypertonic disease and arteriosclerosis of the coronary arteries have been reproduced beforehand. In the latter case, the infarct develops not as an isolated pathological process, existing by itself, but against a background of high blood pressure, hypertrophy of the myocardium and changes in the coronary arteries. In this way, the disease reproduced in experiment considerably resembles the conditions of human infarct of the myocardium.

It is also more valuable to study the mechanisms of the growth of tumors reproduced in animals by taking into account a number of etiological and pathogenic factors, rather than those which develop as the result of an inoculated "ready" tumor. Thus in each case where it is possible and advisable, a model of the whole disease is preferable to models of its partial manifestations.

The models of individual diseases are characterized by a number of peculiarities. First of all, they are of clinicoanatomical type, i. e. when they are used in experiments, it is necessary to reproduce in the animals a disease, which, in one or another way, has an identical clinical and anatomical relation to the same disease in man. For instance, we should not consider that an experimental model of dysentery is general malaise and a number of other disturbances in

the functions (which appear when respective bacteria or their toxins are introduced into the animals), if these disturbances are not accompanied by corresponding morphological changes in the intestines. We are not dealing here with a model of dysentery but with one of intoxication with dysenteric toxins, i.e. not with a model of the disease but only with a model of functional disturbances characteristic of it. In the same way, when we induce in animals a temporary increase in the arterial pressure, which is not accompanied by the hypertrophy of the myocardium and nephrosclerosis, it should be considered only as a model of hypertension and not of hypertonic disease. Another characteristic of models of diseases consists in the fact that, being clinical and pathogenic in type, they are etiological and pathogenic in content, i.e. a certain similarity between man's disease and disease reproduced in animal is not limited to clinical and pathological anatomy, but touches upon certain mechanisms of the appearance and development of the disease. For instance, heart failure induced by mechanical tearing of the valves is accompanied by clinical pictures (murmur) and anatomical pictures (defect of the valves, hypertrophy of the myocardium, edema) typical of this condition. An experiment performed in this way lacks any pathogenic and etiological relation to the processes, which lead to the failure of cardiac valves in man (septic endocarditis, rheumatism and other). The protracted and complicated dynamics of the rheumatic process, gradually leading to valvular failure is in this case compared with an instant action of the metallic hook tearing the valves. By contrast, inducing in animals a polypous and ulcerous endocarditis and cardiac failure by the means of intravenous injections of the culture of *Streptococcus viridens* permits us to obtain not only an anatomical and clinical model but also, to a certain degree, an etiological and pathogenic one. It is not a reproduction of an isolated pathological condition but a disease.

We should add that an etiological similarity of an experimental model with one or another human disease frequently does not have a pathogenic one and vice versa. Let us give some examples. In many methods of inducing experimental pneumonia, relatively large quantities of bacterial culture, causing pneumonia in man, are introduced intratracheally into animals. These experimental models are etiological and not pathogenic since such a mechanism of causing the disease does not correspond to the modern concept of bacterial pneumonias as almost entirely autogenic infections.

Diabetis obtained in experiments with the use of alloxan is a pathogenic model in the sense that at the basis of the disease developing in the animal lie the same affected morphological structures and mechanisms, leading to glycosuria, as in man. At the same time, the two processes have nothing in common etilogically. However, in many cases experimental models reproduce more completely respective human diseases and repeat its etiology and pathogenesis.

In contrast to what we said about models of diseases, the factor of etiological and pathogenic similarity to a respective human disease is often not at all considered in models of general pathological processes, pathological conditions and complications of diseases (inducing heart failure by tearing the valves, nephrosclerosis by injecting Lugol's solution into the renal artery, causing ciliary arrhythmia by applying aconitine solution to the auricle of the heart).

This difference between models of diseases and other types of experimental models explains why the first ones are more universal and more widely used. But models of diseases are not all of the same value; in choosing one or another of them we should clearly understand its limits. For instance, by using certain effects on the parathyroid glands of an animal it is possible to produce in it changes in the bones characteristic of fibrous osteodystrophy. It is possible to study experimentally on osteodystrophic models different problems of etiology, pathogenesis, pathomorphology and treatment of this disease. This can be done because the same relation between an affection of the skeleton and a disturbance in the function and morphology of the internal secretion organ also takes place in man. The same is true of models of hypertonic diseases, traumatic shock, radiation sickness, diffused glomerulonephritis and a number of others. The model of cirrhosis of the liver induced by alimentation (protein and choline insufficiency) is widely spread. It reflects the possibility of a similar etiology and pathogenesis in human cirrhosis and cancer of the liver, thus permitting us to solve the problems of etiology and pathogenesis of this disease and, most important, of its treatment. In contrast, a model of cirrhosis of the liver induced by carbon tetrachloride is not an etiological one, and thus the extent of its use narrows down. This type of model is used for studying the morphogenesis of cirrhosis, the dynamics of restorative processes in the liver, the mechanisms of the development of ascites and splenomegaly, but it is not entirely suitable for experimental research on the etiology, pathogenesis and treatment of this disease because there are no human cases of cirrhosis of the liver caused by such toxins.

One and the same human disease may have several models. This is reflected by the fact that, up to the present, there were several theories on the causes and mechanisms of many human diseases instead of one. For this reason, a model can be created corresponding to each theory on pathogenesis of a given nosological unit. Models of hypertonic disease can serve as an example. It is produced in animals by ischemia of the kidneys, by reacting on different parts of the nervous system, or by disturbing the endocrine balance; this reflects the three main theories of the development in the pathogenesis of this disease, each of the three models occupying its definite place. There are about 10 different models of ulcers of the stomach; each one is based respectively on its proper theory of the pathogenesis of this disease. Therefore, presence of several models of one or another disease does demonstrate that there are no satisfactory ways of reproducing in animals a certain disease but illustrates diverse opinions



on etiology and pathogenesis. When an idea on the causes of a disease changes, then a new model is created to correspond with the new concept. In turn, as soon as the new model of disease is developed on new theoretical prerequisites, it will contribute to further developing the theory on the pathogenesis of this disease. In this way, it was assumed that injury to the renal tissue played an important role in the development of hypertonia and hypertrophy of the myocardium; by experimenting, the phenomenon of high blood pressure after compressing the renal arteries was discovered. The model of this experiment became a new model for this disease and, at the same time, the basis for a new theory on pathogenesis of hypertonic disease. Thus, models of diseases are continuously improving in relation to the evolution in our concepts of one or another disease. Different models of some human disease are being constantly improved and made uniform as is the theory of its pathogenesis. They are gradually approaching their ideal type of a single nosological model of disease.

Many other difficulties, besides those mentioned above, interfere with making nosological models of diseases. They are determined by biological differences of animals and man and, mainly, by the peculiarities in the organization and functioning of the human nervous system. Such illnesses as hypertonic disease, arteriosclerosis, cirrhosis of the liver, chronic pneumonia etc. develop and take their course during many years and even decades whereas, in experiments, their complete cycle usually takes several months, and in rare cases 1-2 years. To use models of diseases successfully several conditions are required. First of all, it is necessary to choose a model which can be reproduced in animals with sufficient continuity. Next, we should have an animal most suitable for this purpose with respect to its size, sex, age and typical characteristics. Thus, when we reproduce in experiments an infectious disease, we should have in mind that, frequently, animals are selectively sensitive to causative organisms of one or another infectious disease. In other cases, one animal should be chosen in preference to other animals susceptible to certain organisms because we can reproduce in him a picture of disease closely resembling the one observed in man. Another example: if the size of animals can be disregarded, then rabbits can be used in preference to dogs for the induction of aneurism. Aneurism can be induced in 100% of the cases of rabbits by tying off the left coronary artery; a dog does not stand this type of experiment, consequently it is difficult to reproduce in dogs this pathological condition. Finally, it is necessary to consider whether an animal of the type selected may be subject to a spontaneous attack of the disease in experiment and if so, how often this may occur. Susceptibility of one or another animal to frequent sickness, such as pneumonia, cirrhosis of the liver, nephrosclerosis and other illnesses could considerably lessen the results of diseases induced in them.

The right choice of the experimental model is an important factor in the successful solution of one or another problem faced by

an experimenter. We should consider all the possibilities which may be encountered in an experiment, and select from experimental models of numerous different types a model providing for the most extensive use of clinical results under given specific conditions. It is only by leaning on the richest factual material of the clinic and by taking from it new ideas and concepts that we can achieve further progress in making experimental models. These in turn will help us to solve current problems of modern medicine.

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